WATER-SWELLABLE POLYMERS

The present invention relates to water-swellable linear polymers, suitable for the production of controlled release compositions for release of pharmaceutically active agents over a prolonged period of time.

Certain cross-linked polyurethane polymers are known from European Patent Publication EP0016652 and EP0016654. These patent specifications describe cross-linked polyurethanes formed by reacting a polyethylene oxide of equivalent weight greater than 1500 with a polyfunctional isocyanate and a trifunctional compound reactive therewith, such as an alkane triol. The resultant cross-linked polyurethane polymers are water-swellable to form a hydrogel but are water-insoluble and may be loaded with water-soluble pharmaceutically active agents. One particular polyurethane polymer is the reaction product of polyethylene glycol 8000, Desmodur (DMDI i.e. dicyclohexylmethane-4,4-diisocyanate) and 1,2,6-hexane triol and which has been used commercially for vaginal delivery of prostaglandins.

However, such polyurethane polymers possess a number of practical disadvantages. Whilst the use of a triol cross-linking agent is effective in providing polymers of relatively reproducible swelling characteristics, the percent swelling is typically 200-300% (i.e. the increase in weight of the swollen polymer divided by the weight of the dry polymer). Pharmaceutically active agents are loaded by contacting the dry polymer with an aqueous

solution of pharmaceutically active agent, such that the solution becomes absorbed into the polymer, forming a hydrogel. The swollen polymer is then dried back to a chosen water content before use. A consequence is that with the conventional cross-linked polyurethane, the degree of swelling limits the molecular weight of the pharmaceutically active agent which can be absorbed into the hydrogel structure to below about 3000. A further disadvantage is that only water-soluble pharmaceutically active agents may be used. Finally, since the conventional cross-linked polyurethane polymer is essentially insoluble in both water and organic solvents, processing of the formed polymer into other solid forms, such as films or coatings, is not possible.

The object of the present invention is to provide a polyurethane polymer of the aforementioned type which is not cross-linked but is linear but which still possesses the desirable properties of reproducible swellability found in the prior cross-linked polyurethanes.

Initial work on the production of linear polyurethane polymers proved unsatisfactory, since the polymers were not stable but continued to react over extended time periods. Also, the swellability was not constant or reproducible, and changed with time.

The present invention is based on the discovery that linear polyurethanes having suitable characteristics may be obtained by reacting a polyoxyethylene glycol with a diol or other difunctional compound and a difunctional isocyanate.

In particular, the present invention provides a water-swellable linear polymer obtainable by reacting together

(a) a polyethylene oxide;

(b) a difunctional compound; and

(c) a difunctional isocyanate.

Alternatively stated, the invention provides a water-swellable linear polyurethane formed of moieties derived from (a),(b) and (c) bonded together.

The linear polymer produced is swellable in water to an enhanced degree, depending upon the ratio of the three components (a),(b) and (c), for example up to 500%, up to 800% or even above 1,000%, thus allowing higher molecular weight pharmaceutically active water-soluble agents to be loaded into the swollen hydrogel derived from the linear polymer. Usually, the polymer is swellable to 200% to 2000%, for example 250 to 1700%. Depending on the particular active agent, swellabilities in the ranges 300-1000, 400-800, 1000-1500, 1100-1300 etc., may be achieved with the polyurethanes of the invention. The linear polymer of the invention is also soluble in certain organic solvents, such as dichloromethane, which allows the polymer to be dissolved and cast into films or coatings. It also allows active agents of poor water solubility but which are soluble in organic solvents, to be loaded into the polymer.

In this description the term "equivalent weight" is used as meaning the number average molecular weight divided by the functionality of the compound.

Polyethylene oxides contain the repeat unit (CH_2CH_2O) and are conveniently prepared by the stepwise addition of ethylene oxide to a compound containing a reactive hydrogen atom. Polyethylene glycols are prepared by the addition of ethylene oxide to ethylene glycol to produce a difunctional polyethylene glycol structure $HO(CH_2CH_2O)_nH$ wherein n is an integer of varying size depending on the molecular weight of polyethylene oxide. Polyethylene oxides used in the present invention are generally linear polyethylene glycols i.e. diols having an equivalent weight of 1500 to 20,000, particularly 3000 to 10,000 and especially 4000 to 8000. Molecular weights are usually in the region 4000 to 35,000.

The difunctional compound is reactive with the difunctional isocyanate, and is typically a difunctional amine or diol. Diols in the range C_5 to C_{20}, preferably C_8 to C_{15} are preferred. Thus, decane diol has been found to produce particularly good results. The diol may be a saturated or unsaturated diol. Branched diols may be used but straight chain diols are preferred. The two hydroxy groups are generally on terminal carbon atoms. Thus, preferred diols include 1,6-hexanediol, 1,10-decanediol, 1,12-dodecanediol and 1,16-hexadecanediol.

The difunctional isocyanate is generally one of the conventional diisocyanates, such as dicyclohexylmethane-4,4-diisocyanate, diphenylmethane-4,4-diisocyanate, 1,6-hexamethylene diisocyanate etc.

The ratio of the components (a) to (b) to (c) (in terms of equivalent weights) is generally in the range 0.1-1.5 to 1 to 1.1-2.5, particularly 0.2-0.9 to 1 to 1.2-1.9. A preferred range is 0.5-0.9 to 1 to 1.5-1.9 Of course, the skilled man through reasonable experimentation would determine the best ratio of ingredients to give the desired properties. The amount of component (c) is generally equal to the combined amounts of (a) and (b) to provide the correct stoichiometry.

Polymers produced at extreme ends of the ranges may not necessarily give optimal properties. For example, high amounts of (a) polyethylene oxide may undesirably lead to the polymer being water-soluble. Small amounts may reduce the percentage swelling. Generally, the ratio of (a) polyethylene oxide to (b) difunctional compound is preferably 0.1 - 1.5 to one, preferably 0.2-0.9 to one.

The polymers are generally produced by melting the previously dried polyethylene glycol together with the difunctional compound (e.g. diol) at a temperature of around 85ºC. A catalyst such as ferric chloride is incorporated. The molten mixture is dried under vacuum to remove excess moisture and the diisocyanate added thereto. The reaction mixture is then poured into billet moulds and cured for a specified time. Thus, the polymer is initially formed as a moulded solid. However, the linear polymers of the present invention are soluble in certain organic solvents. This allows the polymer to be dissolved and the resultant solution cast

to form films. The solution may also be employed for coating granules, tablets etc., in order to modify their release properties. Alternatively, the solution can be poured into a non-solvent so as to precipitate polymer/active microparticles.

Thus, the invention also provides controlled release compositions comprising the linear polymer together with an active agent. The active agent may be a pharmaceutically active agent for human or animal use. It may also be any other agent where sustained release properties (e.g. algicides, fertilisers etc.) are required. The pharmaceutical solid dosage forms include suppositories, pessaries for vaginal use, buccal inserts for oral administration etc. These dosage forms are generally administered to the patient, retained in place until delivery of active agent has occurred and the spent polymer is then removed.

The linear polymer of the present invention may be swollen to a higher degree than the conventional cross-linked polymer and is thus suitable for the uptake of high molecular weight pharmaceutically active agents (up to and exceeding a molecular weight of 3000 e.g. up to 10,000, upto 50,000, upto 100,000 or even up to 200,000 depending on swellability) and is thus particularly suitable for the uptake and delivery of proteins and peptides. Generally, the molecular weight of the active agent is in the range 200 to 20,00. A wide variety of water-soluble pharmaceutically active substances such as those listed in EP0016652 may thus be incorporated.

Furthermore, the linear polymers of the present invention may be loaded with pharmaceutically active agents which are poorly water-soluble, provided that these can be dissolved in a common solvent with the polymer. The resultant solution can then be cast into any desired solid forms. Pharmaceutically active agents of particular interest include:

Proteins e.g. interferon alpha, beta and gamma, insulin, human growth hormone, leuprolide; Benzodiazepines e.g. midazolam; Anti-migraine agents e.g. triptophans, ergotamine and its derivatives; Anti-infective agents e.g. azoles, bacterial vaginosis, candida; and opthalmic agents e.g. latanoprost.

A detailed list of active agent includes H_2 receptor antagonist, antimuscaririe, prostaglandin analogue, proton pump inhibitor, aminosalycilate, corticosteroid, chelating agent, cardiac glycoside, phosphodiesterase inhibitor, thiazide, diuretic, carbonic anhydrase inhibitor, antihypertensive, anti-cancer, anti-depressant, calcium channel blocker, analgesic, opioid antagonist, antiplatel, anticoagulant, fibrinolytic, statin, adrenoceptor agonist, beta blocker, antihistamine, respiratory stimulant, micolytic, expectorant, benzodiazepine, barbiturate, anxiolytic, antipsychotic, tricyclic antidepressant, $5HT_1$ antagonist, opiate, 5HT, agonist, antiemetic, antiepileptic, dopaminergic, antibiotic, antifungal, anthelmintic, antiviral, antiprotozoal, antidiabetic, insulin, thyrotoxin, female sex hormone, male sex hormone,

hormone, antioestrogen, hypothalamic, pituitary hormone, posterior pituitary hormone antagonist, antidiuretic hormone antagonist, bisphosphonate, dopamine receptor stimulant, androgen, non-steroidal anti-inflammatory, immuno suppressant local anaesthetic, sedative, antipsioriatic, silver salt, topical antibacterial, vaccine.

The invention also provides a method of manufacturing the linear polymer by reacting together components (a), (b) and (c).

Embodiments of the present invention will now be described by way of example only in Sections A and B.

TESTS CARRIED OUT ON NEW LINEAR POLYMER

All batches of linear polymer according to the invention were tested as follows.

I. **Appearance.** The polymer should be free of air bubbles.

II. **Percentage Swelling.** Accurately weigh each of ten slices (to 3 decimal places) and note the dry weight (mark each slice with an ID number). Swell the slices in 300ml demineralised water at 25ºC ± 1ºC in a waterbath for 24 hours. Remove slices and blot dry with a paper towel. Reweigh each slice and determine the swelling factor as follows:

$$\%\ \text{Swelling (pph)} = \frac{\text{Swollen weight} - \text{dry weight}}{\text{dry weight}} \times \frac{100}{1}$$

III. **Percent Water Soluble Extractables (% WSE).** Wash thoroughly and dry loss-on-drying vessels in an

oven, overnight at 105ºC, cool for 2 hours in a desiccator and then weight. Record weight to 4 decimal places.

Accurately weigh out 10 slices and put into a 250ml conical flask. Add 150ml demineralised water and swirl gently for 30 seconds. Decant the water and repeat. To the rinsed pessaries add 50ml demineralised water. Shake on a flat bottom shaker for 24 hours at room temperature.

Prepare 2 blanks (water only) and 2 samples (water + extract) each time the determination is carried out. Calculate each individual blank determination and the mean of these two values. This is to be used to obtain the Corrected Total Weight.

Decant the water from the slices and pass <u>ca</u> 10ml of the water (using a plastic syringe) through a Millipore filter (1.2um) into a previously weighted LOD vessel and weigh again. Place in an oven at 105ºC and evaporate sample to dryness (18 hours/overnight). Remove from oven, cool for 2 hours in a dessicator and weigh.

<u>Calculation</u> - (ALL WEIGHTS IN GRAMS)

$$\text{Total Wt of Blank} = \text{Wt of Residue In LOD Vessel} \times \frac{50}{\text{Wt of water added To LOD Vessel}}$$

$$\text{Total Wt of Extract} = \text{Wt of Extract In LOD Vessel} \times \frac{50}{\text{Wt of sample added To LOD Vessel}}$$

Corrected Total Wt = Wt of Extract - Wt of blank

$$\text{\% (w/w) Water Soluble Extractables} = \frac{\text{Corrected Wt of Extract}}{\text{Wt of Pessaries Used}} \times 100$$

IV. **Crystallinity.** Cut a small portion from the slice and seal in a 50ul aluminium pan. Prepare a sealed empty pan of the same dimensions as a reference. Place the pans in the sample and reference holders respectively and run the temperature programme. Calculate the onset temperature and enthalpy using the Data Station. Crystallinity is equal to the ratio of the melt enthalpy of sample to melt enthalpy of 100% crystalline polyethylene oxide, enthalpies expressed in joules/g.

$$\% \text{ crystallinity} = \frac{\text{Enthalpy of sample}}{220.12} \times 100$$

V. **Percentage Swelling 72 hours**

VI. **Percentage Swelling 144 hours**

These percentage-swelling tests were carried out as the standard percentage-swelling test but the total incubation time was increased from 24 hours to either 72 or 144 hours.

Further selective tests included:

VII. Percentage Swelling Over Time

Where three slices of each polymer batch tested were immersed in water and weighed at time intervals over a 24-hour period[10]. The percentage swelling was then calculated from these weights.

VIII. Stability Testing

Samples were tested for stability at 40°C over a four-week period. At the specified time point intervals of one, two and four weeks the percentage swelling (24 hours) was calculated and used as an indication of polymer stability.

IX. Solubility in Different Solvents

Three polymer slices of each batch tested were placed into separate vials for each solvent used. For each batch, the different slices were tested twice using either whole or cut slices and to each vial around 10mL of solvent was added. The solvents used were acetone, dichloromethane, ethanol and methanol.

X. Water Solubility Testing

Ten slices of each batch tested were placed in a conical flask and around 300mL of demineralised water was added. The flasks were placed on a flat bottom shaker for seven days.

SECTION A

A1. POLYMER MANUFACTURE

Various stoichiometric ingredient ratios of PEG:DD:DMDI were used to produce new polymers. Altering the ingredient ratio resulted in a change in the properties of the polymer. PEG is polyethylene glycol; DD is decane-1,10-diol; and DMDI is dicyclohexyl methane-4,4-diisocyanate.

Table 1 New Polymers Manufactured

PEG:DD:DMDI	Batch Numbers
1:1:2 (comparison)	FX02140, FX02143
0.7:1:1.7	FX02158
0.5:1:1.5	FX02148
0.25:1:1.25	FX02141, FX02144, FX02149, FX02161

(The ratio of the known cross-linked polymer FX02139 used for comparison is PEG8000 : hexanetriol : DMDI of 0.8:1.0:2.3)

PEG and DD were weighed into a round-bottomed flask balance and melted overnight at a temperature of 85°C.

The required amount of ferric chloride ($FeCl_3$) plus an excess was weighed into a tared 200mL beaker with spatula. This was made up to 100g with molten PEG/DD from the previous step. This mixture of PEG/DD/$FeCl_3$ was stirred vigorously and kept in the oven at 85°C, with frequent stirring, until required.

The remaining molten PEG/DD was dried under vacuum at 95°C for one and a half hours to remove excess moisture. The moisture content of the PEG/DD was tested using the volumetric Karl Fischer titration method with the specification for moisture being set at no more than 0.05%.

Next, 80g of the PEG/DD/$FeCl_3$ mixture was weighed into a 2L jug and this ensured the correct weight of $FeCl_3$. The amount of PEG/DD required, taking into account the 80g already present from the PEG/DD/$FeCl_3$ mixture, was then

added to the 2L jug which was returned to the oven whilst setting up the equipment in the fume cupboard.

A mixer set at 427 rpm was used to agitate the contents of the 2L jug for 150 seconds, and the DMDI was added during the first 30 seconds.

This final mixture was then poured from the 2L jug into billet moulds, placed in an oven at 95°C and cured for a specified time, which ranged from 10 to 30 hours. After this time, the oven was turned off and the billets left to cool to ambient.

The polymer was then demoulded, and the resultant polymer slabs sliced.

A2. POLYMER PROPERTIES

(a) Characteristics of New Polymer

The characteristics of the new polymer batches manufactured are summarised in Tables 2 - 5.

Table 2 New polymer with a PEG:DD:DMDI ratio of 1:1:2 (Comparison)

	FX00206 (FK)	FX01153 (VJ)	FX01167 (VJ)	FX02140 (SS)	FX02143 (SS)
Cure Time	20 hours 10 minutes	20 hours	20 hours	10 hours	20 hours
Appearance	Normal looking			Normal looking but darker in colour than original polymer	Normal looking but darker in colour than original polymer
Percentage Swelling	646%*	1334.14% RSD 1.82	1918% RSD 2.58	1110% RSD 0.8	1320% RSD 4.37
% WSE	0.35%	2.03%**	7.54%**	1.11%**	1.24%**

* Polymer not sliced but cut into relatively thick slices
** Filtrate too thick for filter paper

It was found that the new polymer with a PEG:DD:DMDI ratio of 1:1:2 lost its integrity during the water soluble extractable testing and one further test of water solubility was carried out on this ingredient ratio to confirm this. These polymers were apparently water soluble to an extent and therefore unsuitable.

Table 3 New polymer with a PEG:DD:DMDI ratio of 0.25:1:1.25

	FX01156 (VJ)	FX02141 (SS)	FX02144 (SS)	FX02149 (SS)	FX02161 (SS)
Cure Time	20 hours	10 hours	10 hours	20 hours	30 hours
Appearance	Golden yellow; undissolved FeCl present; waxy	Golden yellow; undissolved FeCl present; waxy	Normal looking but darker in colour than original polymer	Darker colour than original polymer; undissolved FeCl present	Darker colour than original polymer; some undissolved FeCl
Percentage Swelling	427.41% RSD 0.58	284% RSD 1.09	287% RSD 0.77	304% RSD 0.62	304% RSD 0.35
% WSE	1.23%	0.16%	0.44%	0.24%	0.02%
Crystallinity		43.63% RSD 2.24	43.33% RSD 1.46	44.50% RSD 0.50	44.02% RSD 0.96

Table 4 New polymer with a PEG:DD:DMDI ratio of 0.5:1:1.5

	FX01197 (VJ)	FX02070 (LC)	FX02148 (SS)
Cure Time	20 hours	20 hours	10 hours
Appearance			Darker colour than original polymer; air bubbles present; some undissolved FeCl present
Percentage Swelling	422.4% RSD 0.69	347% RSD 2.6	492% RSD 1.35
% WSE		0.1214%	0.1%
Crystallinity			49.69% RSD 0.47

Table 5 New polymer with a PEG:DD:DMDI ratio of 0.7:1:1.7

	FX02158 (SS)
Cure Time	10 hours
Appearance	Darker in colour than original polymer
Percentage Swelling	730% RSD 0.94
% WSE	0.73%
Crystallinity	49.6% RSD 2.06

(b) Extended Percentage Swelling

Table 6 Results of Swelling at 24, 72 and 114 Hours

Batch Number	Percentage Swelling 24 Hours	Percentage Swelling 72 Hours	Percentage Swelling 144 Hours	Percentage Increase from 24 to 144 Hours
FX02141	284% RSD 1.09	291% RSD 0.51	293% RSD 0.77	3%
FX02144	287% RSD 0.77	299% RSD 0.33	300% RSD 0.51	5%
FX02149	304% RSD 0.62	311% RSD 0.99	318% RSD 1.00	5%
FX02161	304% RSD 0.35	308% RSD 0..43	313% RSD 0.66	3%
FX02148	492% RSD 1.35	504% RSD 1.04	529% RSD 2.20	8%
FX02158	730% RSD 206	786% RSD 3.36	827% RSD 3.36	13%
FX02139 (cross-linked)	308% RSD 0.59		298% RSD 0.76	-3%

(c) Percentage Swelling Over Time is given in Figures 1 and 2:

Figure 1 shows Percentage Swelling Over Time of Two New Polymers (FX02141 and FX02144) Compared With Original Polymer (FX02139); and

Figure 2 shows Percentage Swelling Over Time of Three New Polymers

(d) Stability of Linear Polymer

Table 7 <u>**Stability Testing of FX02150 (Purified FX02144)**</u>

Time	Percentage Swelling
0 (FX02144)	287% RSD 0.77
1 week	370% RSD 4.57
2 week	374% RSD 5.10
4 week	379% RSD 2.81

(g) <u>Solubility Testing of Linear Polymer</u>

Table 8 Solubility Testing of New Polymer in Four Different Solvents

Batch Number	Acetone	Dichloromethane	Ethanol	Methanol
FX02144	Polymer not swollen; slices white and in small pieces; forms suspension on shaking but rapidly sediments	Polymer dissolved resulting in a clear solution	Polymer swollen, slices opaque and intact; slices appear smooth	Polymer swollen & broken up, opaque & still visible – settles to bottom
FX02148	Polymer not swollen; slices white & breaking up	Polymer dissolved resulting in a clear solution	Polymer swollen, slices opaque and intact; slices appear smooth	Polymer dissolved resulting in a clear solution
FX02158	Polymer not swollen; slices white; break up on vigorous shaking	Polymer dissolved resulting in a clear solution	Polymer swollen; slices slightly opaque; appear textured	Polymer dissolved resulting in a clear solution
FX02140	Polymer not swollen; slices white; break up on vigorous shaking	Polymer dissolved resulting in a clear solution	Polymer swollen; slices clear and textured looking	Polymer dissolved resulting in a clear solution

Table 9 Solubility Testing of New Polymer in Water

Batch Number	Results
FX02144	Slices swollen and opaque. No signs of dissolving. Water clear
FX02148	Slices swollen and opaque. No signs of dissolving. Water clear
FX02158	Slices swollen and opaque. No signs of dissolving. Water clear
FX02140	Slices lose their integrity and ultimately dissolve. Water frothy

A3. CONTROLLED RELEASE COMPOSITIONS

Dissolution Testing

A dosage form when placed into a vessel containing liquid media will release drug in a defined manner dictated by the formulation. This process known as dissolution can be used as an in vitro marker of the mechanism of release in the body. Sampling is carried out at regular intervals over a period of several hours and the amount of drug in the samples is analysed by spectrophotometer or HPLC. The data are normally represented as the release of labelled content against time.

(i) Pilocarpine

Potency

Ten units are swollen, macerated and quantitatively extracted into 500ml of mobile phase. Pilocarpine is then assayed by HPLC relative to a reference standard. Detection is by UV spectrophotometer. The method is capable of detecting pilocarpine and its main degradation products, pilocarpic acid, iso-pilocarpine and iso-pilocarpic acid. The method is based upon the European Pharmacopeia method for pilocarpine.

Dissolution

Pilocarpine in vitro release from the units is performed by a USP paddle method at 50 rpm, 37ºC. The pilocarpine released is assayed by HPLC as in the potency method.

Loading

The blank polymer slices are placed in purified water and agitated at about 4ºC for approximately 16-20 hours; the water is then decanted. Water swollen polymer slices are placed in an ethanol:water solution and agitated at about 4ºC for approximately 6-8 hours. The slices are then dried. Pilocarpine is dissolved in water which is then added to the dry polymer slices. The slices and drug loading solution are agitated at approximately 4ºC for approximately 16-20 hours to allow the uptake of drug. At the end of the dosing period the remaining drug solution is decanted and the swollen polymer slices are dried for 18-28 hours.

Polymer batch FX02144 was purified (FX02150) and then loaded with pilocarpine (FX02151).

Figure 3 shows normalised graph of percentage Pilocarpine released against time for linear polymer FX02151 compared with original polymer FX01234 and FX01194

(ii) Loading with PGE_2 (Dinoprostone)

Potency

Ten units are swollen, macerated and quantitatively extracted into 500ml of mobile phase. Dinoprostone is then assayed by HPLC relative to a reference standard. Detection is by UV spectrophotometer. The method is capable of detecting Dinoprostone and its main degradation products, PGA2, 8-iso PGE2 and 15 keto-PGE2. The method is based upon the EP method for dinoprostone.

Dissolution

Dinoprostone in vitro released from the units is performed by a USP paddle method at 50rpm, 37ºC. The dinoprostone released is assayed by HPLC as in the potency method.

Purification and Loading

The blank polymer slices are placed in purified water and agitated at about 4ºC for approximately 6-8 hours, then the water is decanted. The swollen slices are again placed in purified water and agitated at about 4ºC for approximately 16-20 hours; the water is then decanted. Water swollen polymer slices are placed in an ethanol:water solution and agitated at about 4ºC for approximately 6-8 hours. A solution of Dinoprostone is made by dissolving the appropriate amount of Dinoprostone in ethanol. The resulting solution is added to water and ethanol. This makes up the drug loading solution which is then added to the swollen polymer slices to give a 25% w/w ethanol:water mix. The slices and drug loading solution are agitated at approximately 4ºC for approximately 16-20 hours to allow the uptake of drug. At the end of the dosing period the remaining drug solution is decanted and the swollen polymer slices are dried for 18-28 hours.

Prostaglandin E_2 was loaded by an analogous process into a batch of cross-linked polymer (FX02139, loaded FX02159) and a batch of linear polymer (FX02144, loaded FX02157),

both with 0.6mm thick slices. The measured potencies were 9.4mg (FX02159, control) and 9.7mg (FX02157) respectively.

Figure 4 shows PGE_2 release profiles of cross-linked polymer and new linear polymer.

A4. <u>MANUFACTURE OF FILMS</u>

In initial experimentation into film manufacture, six vials were set up containing one, two, three, four, five and eight slices of polymer respectively. The polymer batch used was FX02141. To each vial around 10mL of dichloromethane was added. All vials were sonicated until the polymer dissolved. The resultant solutions were poured onto a watchglass (20cm diameter) and allowed to dry in a fume cupboard uncovered.

In further film development work, the amounts of polymer and solvent were weighed into a suitable glass container, which was then sealed and sonicated until the polymer dissolved. Some films were poured on a watchglass as before, whilst others were poured in a petri dish (8cm diameter). To control the drying of the films, some solutions poured were covered with a 1L glass beaker.

Films were also manufactured using a doctor blade, with the solution being poured onto a glass plate in a fume cupboard and spread along the length of the plate.

Table 10 Initial Film Manufacture Results

Number of Slices of FX02141 in 10mL Dichloromethane (DCM)	Notes on Resultant Film
1	Lots of small air bubbles. 0.023mm thick
2	Removed from glass too quickly and film was self adhesive and formed a clump of sticky polymer
3	Air bubbles present from shaking which leads to holes in film. Film opaque in colour. 0.083mm thick
4	Smooth, opaque film; some air bubbles. Around 8cm in diameter. 0.112mm thick
5	Good film that looks uniform on one side but half was partially stuck together due to being removed from watchglass before it was fully dry. 0.133mm thick
8	Very strong film; air bubbles a problem. Oval in shape – 7cm by 5cm. 0.354mm thick

The film made with five slices of polymer in solvent was swollen in demineralised water in a plastic petri dish. The swollen form of the film was found to be strong. The film was placed on a watchglass to dry. Once dried, the film regained its shape and strength.

Table 11 <u>Films Manufactured Using Polymer Batch FX02141 Dissolved in Dichloromethane</u>

Vial	Weight FX02141 (g)	Weight DCM added (g)	%w/w Polymer in DCM	Details
1	0.8911	12.763	6.98	Loaded with cresol red.
2	0.9478	13.806	6.87	Loaded with bromophenol blue
3	0.7897	14.797	5.34	Poured onto watchglass with another watchglass placed on top; film not uniform
4	0.9238	10.661	8.67	Poured onto watchglass; film used for swelling over time test
5	0.9572	15.936	6.01	Poured onto watchglass, covered with a 1 litre beaker; film uniform
6	0.8679	13.899	6.24	Poured into a glass petrie dish, covered with beaker; uniform film; film used for crystallinity testing; film brittle
7	0.9751	15.286	6.38	Poured in a glass petrie dish, covered with beaker; film brittle
8	1.0680	11.193	9.54	Made into a 53.20%w/w solution of ethanol in DCM/polymer mixture; didn't go into a film
9	1.0618	13.335	7.96	Loaded with bromophenol blue; film swollen
10	0.8490	11.557	7.35	Made into a 34.73%w/w solution of acetonitrile in DCM/polymer mixture; film brittle – opaque looking
11	0.6528	10.029	6.51	Made into a 45.00%w/w solution of methanol in DCM/polymer mixture
12	0.9013	6.541	13.78	Made into a 108%w/w solution of acetone in DCM/polymer mixture, poured onto watchglass and covered with beaker; film not uniform

Portions of films made from Vials 1 and 2 were cut and placed into vials of demineralised water to determine whether the film could release the loaded dye.

Table 12 <u>**Films Manufactured Using Polymer Batch FX02158 in Different Solvents**</u>

Vial	Weight FX02158 (g)	Weight Solvent Added (g)	%w/w Polymer in Solvent	Details
A	0.7677	10.0211g methanol	7.66	Non-uniform: one large clearer patch visible; feels smooth; opaque film; slightly textured looking
C	0.7755	15.9041g dichloromethane	4.88	Uniform in appearance; opaque film covered in small clear spots all over; feels rough; not brittle
E	0.7631	9.6095g dichloromethane and 4.9686g methanol	5.23	Uniform film; smooth to touch; very brittle and breaks on touching; opaque film covered in clear spots which are smaller and more spread out than vial c

The polymer in vials C and E began dissolving immediately, whereas vial A was slower. The solutions from these vials were poured into separate glass petri dishes in a fume cupboard and each covered with a one-litre beaker. They were left until dry. It was noticed that the solution from vial c dried quicker than that of vials a and e.

Table 13 Films Manufactured to Compare Drying Techniques

Duran	Weight Polymer (g)	Weight DCM (g)	%w/w polymer in DCM
1	1.9542 FX02158	37.2	5.25
2	1.9806 FX02158	35.6	5.56
3	1.8595 FX02144	40.0	4.65
4	1.8508 FX02144	37.0	5.00

The solutions from all four durans were poured separately into glass petri dishes in a fume cupboard.

Durans 1 and 3 were covered with a one-litre glass beaker, and durans 2 and 4 were left uncovered.

Films from durans 1 and 3 feel rough to touch, whereas films from durans 2 and 4 are smooth. Film from duran 2 has a rougher patch at one side.

All films manufactured from durans 1-4 were of comparable strength and none were brittle.

Two films were manufactured using the doctor blade. Both polymers used were dissolved in DCM (about 5% w/w) to make the solution, and both solutions were poured onto the same glass dish under the same conditions.

The film manufactured with polymer FX02144 was brittle and fell apart on storage whereas the film made with FX02158 (which was loaded with bromophenol blue for a demonstration) remained intact.

To access the release of a drug from a polymer film, the percentage swelling over time was calculated. This was graphically represented, using the percentage swelling over time of the polymer slice of same batch used in film manufacture as a reference. The results are shown in Figure 5.

The average weight of a film portion used was 0.0272g; and the average weight of a polymer slice (FX02141) was 0.1381g.

A5. DISCUSSION

a. Appearance

During appearance testing, it was observed that new linear polymer billets were slightly darker in colour when compared to known cross-linked polymer billets. This was accounted for by comparing the $FeCl_3$ content in both. It was calculated that known cross-linked polymer contained 0.01% w/w $FeCl_3$ in PEG whereas linear polymer had 0.0266% w/w $FeCI_3$ in PEG.

b. Cure Time

Previous linear polymers were manufactured with a 20 hour cure time, however batches FX02140 and FX02141 were manufactured with a 10 hour cure time.

By comparison of two batches with the same ingredient ratio but different cure times [FX02140 (10 hour cure time) and FX02143 (20 hour cure time)], it was seen that a cure time of 10 hours produced more promising results

with a lower RSD for percentage swelling test and a lower percent water soluble extractables. As a result, a 10 hour cure time was then used for batches FX02144, FX02148 and FX02158.

However, the effect of cure time was further investigated using batches FX02141, FX02149 and FX02161 with cure time of 10, 20 and 30 hours respectively. By comparison of results from these three batches, it was found that there was no correlation in crystallinity; % WSE decreased as the cure time increased and the percentage swelling for FX02144 is about 20% less than the swellings of FX02149 and FX02161 which are identical. The RSD for percentage swelling decreased are cure time increased.

c. Ingredient Ratio

Polymer manufactured with a PEG:DD:DMDI ratio of 0.25:1:1.25 was shown to have the same characteristics as the cross-linked polymer, with all results within the known cross-linked polymer specifications.

The linear polymer according to the invention meets these specifications and the results are reproducible. Furthermore, the linear polymer is soluble in certain solvents whereas the known cross-linked polymer is insoluble.

The known cross-linked polymer, with a percentage swelling of around 300%, cannot be loaded with drugs of high molecular weight, such as peptides and proteins.

In comparison, a linear polymer of the present invention, FX02158 (PEG:DD:DMDI 0.7:1:1.7), was shown to have a percentage swelling of 730% and insoluble in water.

d. Swelling Profile

As the ratio of PEG:DD increased, the percentage swelling at 24 hours also increases. The accepted percentage swelling test for the known cross-linked polymers in 24 hours. This was extended to 72 and 144 hours for the polymer according to the invention to ascertain the time required for the polymer slice to reach maximum swelling.

With higher rations of PEG:DD, it was found that the percentage swelling increased by a larger difference between 24 and 144 hours when compared to polymers with a low PEG:DD ratio. There was a 3% increase in percentage swelling of FX02141 (PEG:DD 0.25:1) from 24 to 144 hours compared to a 13% increase in FX02158 (PEG:DD:0.7:1).

Polymers with higher PEG:DD ratios have not reach their maximum percentage swelling by 24 hours. This is confirmed by percentage swellings over time curves (Figure 2). Polymer slices with a PEG:DD ratio of 0.25:1 reach their maximum swelling by around 5 hours when the curve plateaus, however, polymer slices with a higher PEG:DD ratio of 0.7:1 it was seen that the percentage

swelling was increasing at 144 hours with the gradient of the curve at this point being positive.

e. Stability

Stability testing at 40°C was carried out on FX02150 (purified FX02144) over a period of 4 weeks. The results have shown that the percentage swellings increased with time and this is comparable to results of cross-linked polymers at 40°C.

f. Drug Release

Polymer batch FX02144 (PEG:DD:DMDI 0.25:1:1.25) was loaded with pilocarpine and PGE_2. This polymer has similar characteristics to cross-linked polymer and therefore, release profiles of both drugs from the two different polymers could be compared.

The release characteristics of pilocarpine were shown to be comparable between linear and cross-linked polymer. This was confirmed by comparison of percentage swelling over time of the linear batch with cross-linked polymer (Figure 1) where the rate of swelling was the same for both.

However, PGE_2 release was found to be different. The linear polymer released the drug slower than the cross-linked polymer.

g. Solubility Testing

Four different polymers, with different ingredient ratios, were manufactured and none of these polymers were soluble in ethanol or acetone.

FX02144 was insoluble in methanol, whereas other batches tested were soluble in this solvent.

All batches tested were soluble in dichloromethane.

h. Film Preparation

From initial experimentation a promising combination of polymer and solvent was found to be 4-5 slices (approx equivalent to 0.7g polymer) in 10mL DCM. This was scaled up to 13 slices in 30mL DCM and the film manufacture was shown to be reproducible with similar films achieved using this combination.

A manufactured film was swollen in demineralised water and the swollen form was found to be strong and stretchy. This swollen film was then removed from the water and allowed to dry. Once dried the film regained its shape and strength.

On further film development, the film was tested to determine whether it could release a loaded dye. Portions of films loaded with dye were submerged in water, and the water colour changed over time showing

that the film had the ability to release a loaded substance.

It was discovered that a film manufactured by dissolving the polymer in different solvents had an effect on the total drying time of the film, the uniformity, texture and strength of the final film. In addition, the technique used to dry the films had an effect on its final appearance in terms of uniformity and texture.

The percentage swelling over time of a polymer film produced was calculated, and compared to the percentage swelling over time of the polymer slices used to make the film. As expected, the portions of film reached their maximum percentage swelling much quicker than the polymer slice because the thickness and average weight of the film portions were much less than the polymer slices. This can be used as an indication of release rate of a drug from a polymer film.

SECTION B

B1 POLYMER MANUFACTURE

Various type of polyethylene glycols, diols and diisocyanates, and various stoichiometric ratios of these compounds were used to further demonstrate their effects on the properties of the new polymer. PEG4000, PEG8000, PEG12000 and PEG35000 are polyethylene glycols having molecular weight of 4000, 8000, 12000 and 35000,

respectively; HD is 1,6-hexanediol, DD is 1,10-decanediol, DDD is 1,12-dodecanediol and HDD is 1,16-hexadecanediol; DMDI is dicyclohexylmethane-4,4-diisocyanate and HMDI is 1,6-hexamethylene diisocyanate.

Polymers, except batch numbers BP03007, BP03014 and BP03015, were produced with the same polymerisation method as in Section A. The only difference was that the melted PEG and diol mixture was mixed for 30 mins. in a rotavapor, before 100g was taken out to make a catalyst mixture to produce a more homogenous mixture.

For polymerisation of PEG35000 (batch numbers BP03007 and BP03014) the polymerisation reactor was changed to a stirring tank reactor (700 ml) and the polymerisation temperature was increased to 140°C to reduce the melt viscosity of the PEG. PEG was dried overnight in a rotavapor using vacuum and 50 °C temperature. PEG, diol and ferric chloride were fed to a stirring tank glass reactor. The mixture was melted for 2 hours under nitrogen using a 140°C oil bath. Mixing was turned on for 30 min before diisocyanate was fed to the reactor and then mixed for 5 min. Polymer was poured to the preheated mould (130°C) and kept for 10 hours in an oven at 95°C. After this time, the oven was turned off and the polymer billets were left to cool to room temperature. The polymer billets were then demoulded and sliced.
A two-step polymerisation method was also used to produce more controlled polymer structure (batch number BP03015). PEG was dried overnight using vacuum and 50°C in a

rotavapor. Diisocyanate was first fed to the stirring tank reactor. Then about 40g PEG with ferric chloride on the top of it was fed to the reactor. The reactor was heated to 95°C and PEG was fed to the reactor during 3 hours by using about 20g portions at the each time. Mixing (30 rpm) was turned on when the reactor temperature reached 95°C. Then the diol was fed to the reactor and mixing increased to 60 rpm and mixed for 5 min. Polymer was poured into the preheated mould (95°C) and kept for 10 hours in an oven at 95°C. After this time, the oven was turned off and the polymer billets were left to cool to room temperature. The polymer billets were then demoulded and sliced.

B2. <u>POLYMER PROPERTIES</u>

The effects of type and ratios of polyethylene glycols, diols and diisocyanates on the properties of polymers can be seen in Tables 14-18.

Table 14 Molar ratios between PEG 8000 and 1,10-decanediol was changed.

Batch Number	03032	03030	03031	03033
PEG 8 000 (Molar Ratio)	0.9	0.7	0.7	0.1
DD (Molar Ratio)	1	1	1	1
DMDI (Molar Ratio)	1.9	1.7	1.7	1.1
Cure Time	10	10	10	10
Percentage Swelling (%)	1048	612	750	178
WSE (%)	2.3	1.0	1.4	2.3
Tm (°C)	62.4	61.4	62.4	54.9
Crystallinity (%)	48.6	52.7	49.3	33.1
Soluble in DCM	yes	yes	yes	yes
Soluble in THF	no	no	no	yes

DD is 1,10-decanediol
DMDI is dicyclohexylmethane-4,4-diisocyanate
WSE is water soluble extractable

Table 15. The length of PEG was changed.

Batch Number	Bp03001	03031	BP03005	BP03007	BP03014
PEG (MW)	**4 000**	**8 000**	**12 000**	**35 000**	**35 000**
PEG (Molar Ratio)	0.7	0.7	0.7	0.7	0.1
DD (Molar Ratio)	1	1	1	1	1
DMDI (Molar Ratio)	1.7	1.7	1.7	1.7	1.1
Cure time	10	10	10	10	10
Percentage Swelling (%)	395	750	993	Lost Intergrity	742
WSE (%)	1.3	1.4	N.D.	WS	CH
Tm (°C)	53.8	62	64.0	65.7	65.3
Crystallinity (%)	36.3	49.3	46.5	64.7	46.4
Soluble in DCM	yes	yes	yes	yes	yes
Soluble in THF	yes	no	no	no	no

MW is molecular weight
DD is 1,10-decanediol
DMDI is dicyclohexylmethane-4,4-diisocyanate
WS water soluble
CH changes in shapes

Table 16. The length of diol and the amount of diol was changed.

Batch Number	03035	03031	Bp03002 /1	03036	03034	BP0300 6
Diol	HD	DD	DDD	DDD	DDD	HDD
PEG 8 000 (molar ratio)	0.7	0.7	1.5	0.9	0.7	0.7
Diol (molar ratio)	1	1	1	1	1	1
DMDI (molar ratio)	1.7	1.7	2.5	1.9	1.7	1.7
Cure Time	10	10	10	10	10	10
Percentage Swelling (%)	899	751	1679	602	640	470
WSE (%)	0.92	1.4	5.7	0.7	0.89	N.D.
Tm (°C)	61.8	62	61.1	60	60.6	60.1
Crystallinity (%)	52.8	49.3	48.7	43.1	38.2	45.8
Soluble in DCM	yes	yes	yes	yes	yes	yes
Soluble in THF	no	no	no	no	no	no

HD is 1,6-hexanediol
DD is 1,10-decanediol
DDD is 1,12-dodecanediol
HDD is 1,16-hexadecanediol
DMDI is dicyclohexylmethane-4,4-diisocyanate

Table 17. The effect of diisocyanate.

Batch Number	03031	BP0300 3
Diisocyanate	**DMDI**	**HMDI**
PEG 8 000 (molar ratio)	**0.7**	**0.7**
DD (molar ratio)	**1**	**1**
DMDI (molar ratio)	**1.7**	**1.7**
Cure Time	10	10
Percentage Swelling (%)	751	1070
WSE (%)	1.4	N.D.
Tm (°C)	62	63.4
Crystallinity (%)	49.3	52.2
Soluble in DCM	yes	yes
Soluble in THF	no	no

DMDI is dicyclohexylmethane-4,4-diisocyanate
HMDI is 1,6-hexamethylene diisocyanate

Table 18 Two-step Polymerisation method

Batch number	**BP0301 6**
PEG 8 000 (molar ratio)	0.7
DD (molar ratio)	1
DMDI (molar ratio)	1.7
Cure Time	10
Percentage Swelling (%)	1750
WSE (%)	N.D.
Tm (°C)	61.2
Crystallinity (%)	52.4
Soluble in DCM	yes
Soluble in THF	no

DD is 1,10-decanediol
DMDI is dicyclohexylmethane-4,4-diisocyanate

B3 CONTROLLED RELEASE COMPOSITIONS

Linear Polymer Characterisation & Drug Loading Examples

Batches of linear polymer (03030, 03032 and 03033), together with cross-linked polymer batch 03003 (polymer ratio PEG 8000 : hexanetriol : DMDI of 1.0 : 1.2 : 2.8) for comparison were sliced to produce polymer slices of dimension 10mm x 30mm x 1.0mm. The polymer slices were purified at 25°C using three washes in purified water and/or purified water/ethanol. Next, all slices were dried under vacuum.

Five drugs namely clindamycin phosphate, oxytocin, terbutaline sulphate, misoprostol and progesterone were loaded into the various polymers. These drugs were

chosen as they covered various aspects such as highly water soluble, poorly water soluble, peptides, steroids and lower molecular weight molecules.

The drugs were loaded into the polymer by dissolving each drug candidate into a suitable solution, immersing the polymer slices for an appropriate time then removing from the solution and drying. Table 19 details the loading parameter and conditions.

Table 19 Loading parameters for various drug candidates

Drug	CLI	OXY	TBS	MIS	PRO
General					
Batch no.					
• A03003 (CLP)	CL 03009	OX 03001	FX 02248	MS 03025	PG 03002
• A03030 (LP)	CL 03017	OX 03002	TB 03001	MS 03030	–
• A03032 (LP)	CL 03020	OX 03003	TB 03002	–	–
• A03033 (LP)	–	–	–	MS 03033	PG 03003
Drug content/unit	70 mg	1 mg	10 mg	200 µg	10 mg
Drug solubility (in water)	Very soluble (500 mg/ml)	Very soluble	Soluble (250 mg/ml)	Insoluble (3 mg/ml)	Insoluble (< 0.4 mg/ml)
No. of pessary (n)	18 - 23	18 - 23	18 - 23	18 - 23	18 - 23
Loading					
Loading solution	4.76% w/w NaCl solution	PBS solution (pH 7.4)	Purified water	25% w/w EtOH solution	75% w/w EtOH solution
Loading temperature	25°C	25°C	25°C	4°C	25°C
Incubation					
Incubation temperature	25°C	25°C	25°C	4°C	25°C
Incubation duration	16-24 hours	16-24 hours	16-24 hours	16-24 hours	16-24 hours
Drying					
Drying method	Vacuum oven	Vacuum oven	Vacuum oven	Vacuum oven	Rotavapor
Drying temperature	Room temperature	Room temperature	Room temperature	Room temperature	Room temperature
Drying duration	≥ 72 hours (as required)	≥ 24 hours (as required)	≥ 24 hours (as required)	≥ 24 hours (as required)	≥ 24 hours (as required)

Abbreviations:
CLI – Clindamycin phosphate; OXY – Oxytocin; TBS – Terbutaline sulphate; MIS – Misoporstol; PRO – Progesterone; NaCl – Sodium chloride; PBS – Phosphate buffered saline; EtOH – Ethanol

The drug loaded polymer were analysed for in vitro drug release following USP Method XXIII, Apparatus 2 at 37°C, with 50rpm paddle speed. Drug release was analysed by ultraviolet spectroscopy or high pressure liquid

chromatography (HPLC) as appropriate. Various dissolution parameters or settings are summarised in Table 20.

Table 20 Dissolution parameters and settings

Drug	CLI	OXY	TBS	MIS	PRO
Dose per unit (mg)	70	1	10	0.2	10
Dissolution volume, V (ml)	900	100	250	250ml	900
Dissolution media	Water	Phosphate buffer solution (pH 7.4)	Water	Water	Water
Wavelength, λ (nm)	210	562	276	280 (after derivitisation)	249

Abbreviations:
CLI – Clindamycin phosphate; OXY – Oxytocin; TBS – Terbutaline sulphate; MIS – Misoporstol; PRO – Progesterone; NA – Not available

Figure 6 to 10 show the mean dissolution profiles of each drug candidate from the various polymers.

The effect of drug type on mean dissolution profile of linear polymer batch A03030 is shown in Figure 11.

Rate of drug release *k* values of each dissolution profile was determined by calculating the slope of graph % drug release versus square root time. All the linear relationship between % drug release and square root time has R^2 correlation value > 0.95%. Rate of drug release *k* from the dissolution profiles of each drug candidate from various pessaries are shown in Table 21.

Table 21 Rate of drug release (k minutes$^{-1/2}$) of drug candidates from cross-linked and linear polymer pessaries

Water solubility (mg/ml)	Molecular weight	Drug	Rate of drug release, k (minute$^{-0.5}$)			
		Polymer type	*A03003 (CLP)*	*A03033 (LP)*	*A03030 (LP)*	*A03032 (LP)*
		% Swelling (in water)	***295.4***	***230.0***	***678.9***	***1202.8***
500	505	CLI	10.701	-ND-	12.765	12.380
Very soluble	1007	OXY	6.749	-ND-	7.875	7.85
250	274	TBS	13.628	-ND-	13.262	11.954
3	383	MIS	4.507	2.213	4.378	-ND-
< 0.4	315	PRO	2.414	1.256	-ND-	-ND-

Abbreviations:
CLI – Clindamycin phosphate; OXY – Oxytocin; TBS – Terbutaline sulphate; MIS – Misoporstol; PRO – Progesterone; CLP – Cross-linked polymer; LP – Linear polymer; ND – No data